DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(12), 2111-2145 (1987)



# TABLET DISINTEGRATION UPDATE: THE DYNAMIC APPROACH.(*)

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## BACKGROUND

When, a few years ago, we started investigating tablet disintegration, what appeared most appealing to us was the dynamic aspect of the disintegration process.

In the first paper published by our group on tablet disintegration, it was stated that: "to obtain a rapid disintegration, which is a necessary condition for a high bioavailability of the active ingredient, a disintegrating force must develop inside the tablet, capable of weakening and breaking

(*) Presented at 6th Pharmaceutical Technology Conference, Canterbury (England), April 1987

interparticle bonds. This force is generated by the replacement of solid/air with liquid/solid interfaces..." (1).

At that time, List was publishing a series of very interesting articles dealing with the measurement of swelling pressure inside disintegrating tablets (by means of a strain gauge based apparatus) (2,3) and he was able to conclude that the pressure development was linked to the presence of a swelling disintegrant and responsible for the disintegration process. Although it was clear that swelling pressure was not the same as swelling volume, no definite relationship could be found between swelling pressure and disintegration time. Since this early work, many papers have been published on this subject by our group and further research is going on, that we will attempt to summarize.

## DISINTEGRATING FORCE MEASURES

During our research we also developed an apparatus for the measurement of disintegrating force (4) (Fig. 1).
Basically it consisted of a tablet holder (an empty stainless steel cylinder closed at its lower end by a sintered glass disc) and a piezoelectric quartz load-washer (Kistler) connected to a

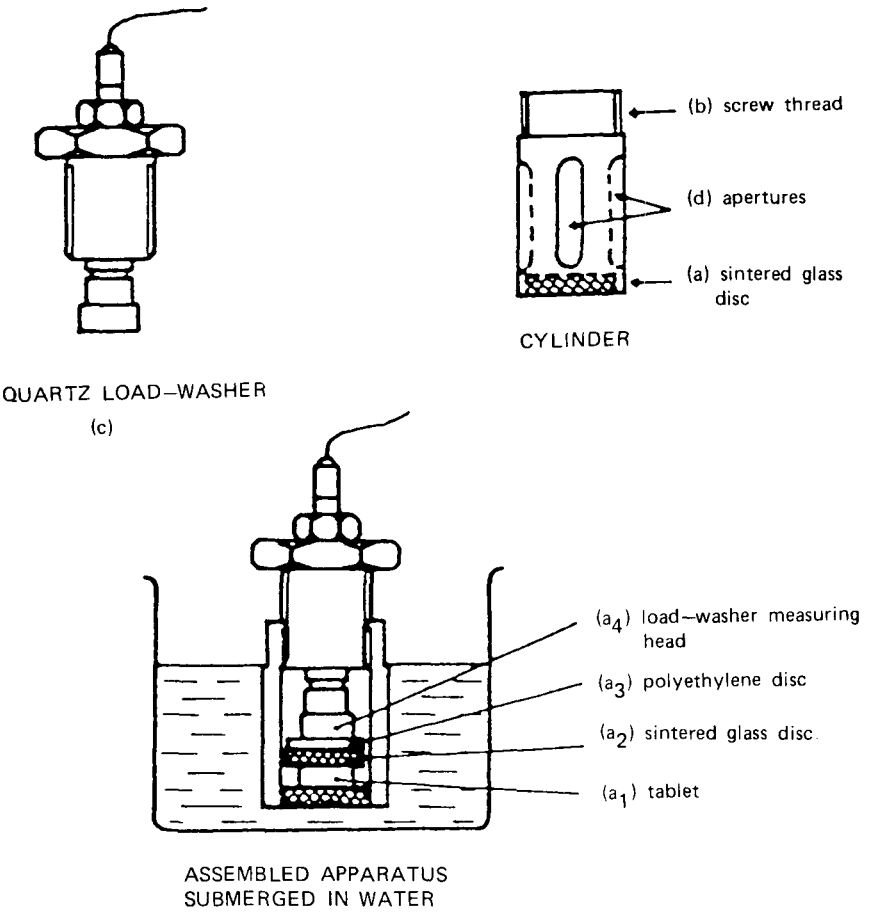


FIGURE 1

Apparatus for disintegrating force measurement (4).

X-Y recorder. To effect force measurements, the tablet, whose sides were opportunely covered with a waterproof scotch tape, was placed on the sintered glass disc and the tablet holder screwed on to the transducer. When the assembled apparatus was submerged in the immersion fluid, the tablet was invaded from its lower

face and the force developing inside it was transmitted in the axial direction to the load-washer, whose opportunely amplified signal was fed to the recorder where the disintegrating force versus time curve was displayed.

The apparatus was constructed so as to avoid radial losses of disintegrating force, to assure an even water uptake from the lower face and to assure a complete transmission of the force developing inside the tablet.

In a later version (5) the piezoelectric load-washer was replaced by a load cell and the disintegrating force data was collected in a computer memory (Minc 11 Digital).

In order to further List's findings, our approach was to examine the entire disintegrating force development kinetics.

Since the early force experiments were run, we attempted to describe the entire force versus time curve by means of the following hyperbolic equation written in the simplified form (4):

$$\frac{x}{y} = \frac{x}{y_0} + \frac{b}{y_0}$$

where x represents the time, y the force and $y_0$ and b represent the maximum force developed and the time needed for developing half maximum force, respectively. From these two parameters, the

value $-\frac{y_0}{2b}$ could be calculated, which represents a mean disintegrating force development rate value.

Subsequently, using a computer program run on a Digital Minc 11 (6), disintegrating force versus time curves were fitted according to the Weibull distribution function, as described for dissolution (7), rearranged into the form:

$$\log \left[ - \ln (1 - F/F_\infty) \right] = b \log (t - t_0) - b \log t_d$$

where F is the disintegrating force developed at time t and $F_\infty$ is the maximum force developed; $t_0$ is the time lag; b represents the shape parameter of the curve and depends on whether a sigmoidal, a single first order exponential or an initially steaper exponential curve is considered; $t_d$ represents the time parameter of the distribution and represents the time needed to obtain 63.2% of maximum disintegrating force starting from the end of lag time $t_0$ .

These parameters, obtained according to the fitting procedure described in (6), allowed a complete characterization of the saturation curves obtained. Moreover a rate parameter termed "input" (that is the derivative of the Weibull equation at time $t = t + \tau_d$) was calculated from the fitted curve.

"Input" represents an instantaneous value of disintegrating force

development rate and was believed to be more informative of the kinetics of force development.

## DISINTEGRATING FORCE AND DISINTEGRATION PROPERTIES

We had put forward the hypothesis (1) that not only the maximum disintegrating force but also the time needed to attain the maximum force development was relevant to the disintegration velocity.

As data on disintegrating force became available, this hypothesis was given further support.

In one of our early papers (4), differing series of acetylsalicylic acid (ASA) and ASA coated tablets, prepared under controlled conditions, were examined for disintegrating force development. In fact, a linear correlation was found, on a log-log scale, between the disintegration time and the $\frac{y_0}{2b}$ value, that is the mean value of the disintegrating force development rate (Fig. 2).

In a subsequent paper (6) differing series of ASA coated tablet formulations containing differing disintegrants or disintegrant mixtures in various percentages were prepared and examined in detail for force development (Table 1). We observed

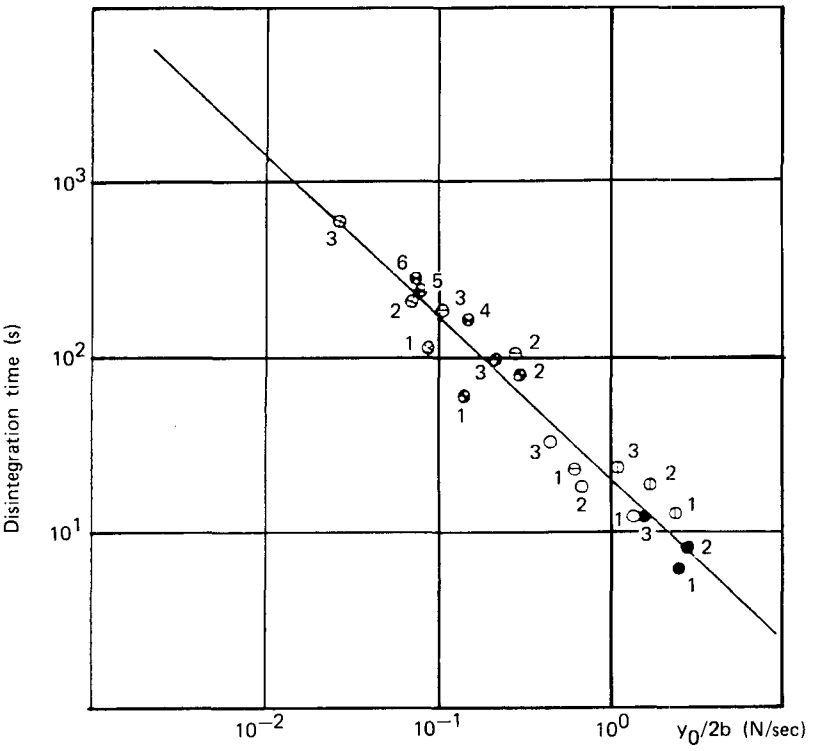


FIGURE 2

Relationship between mean disintegrating force development rate ($y_0/2b$) and disintegration time (4).
(Symbols refer to differing ASA and ASA coated formulations and figures indicate the increasing order of compression force within a formulation).

that a high value of maximum disintegrating force ($F_\infty$) does not always correspond to a fast disintegration. For example, although mixtures G and A show comparable maximum disintegrating force values (at the highest compression force levels) their disintegration times are markedly different. In this case, $\tau_d$

## TABLE 1

Disintegration time and disintegrating force parameters of different ASA coated tablets (6).
The composition of mixtures (g/tablet) is given below.

| Mixture | Compression Force, hN | Disintegration Time, s | Disintegrating Force ($F_d$), N | $\tau_d$, s | Shape Parameter ($b$) |
|---|---|---|---|---|---|
| A | 43 | 18 | 14 | 3 | 1.3 |
| | 79 | 18 | 18 | 2 | 1.0 |
| | 154 | 19 | 31 | 6 | 1.0 |
| | 186 | 18 | 34 | 7 | 0.7 |
| | 280 | 19 | 34 | 8 | 0.7 |
| B | 56 | 18 | 26 | 8 | 1.3 |
| | 93 | 16 | 33 | 8 | 1.2 |
| | 145 | 17 | 40 | 11 | 1.1 |
| | 196 | 20 | 42 | 14 | 1.0 |
| | 251 | 25 | 43 | 20 | 1.1 |
| C | 53 | 146 | 4 | 70 | 0.6 |
| | 72 | 256 | 5 | 140 | 0.7 |
| | 135 | 964 | 5 | 610 | 1.0 |
| | 164 | 1223 | 6 | 840 | 1.3 |
| | 287 | 1695 | 5 | 990 | 1.2 |
| D | 50 | 20 | 37 | 9 | 1.1 |
| | 102 | 27 | 51 | 18 | 1.2 |
| | 135 | 32 | 56 | 21 | 1.4 |
| | 193 | 41 | 58 | 29 | 1.2 |
| | 274 | 53 | 52 | 42 | 1.5 |
| E | 66 | 9 | 34 | 5 | 0.9 |
| | 89 | 10 | 42 | 5 | 0.9 |
| | 130 | 12 | 47 | 8 | 0.8 |
| | 170 | 16 | 53 | 11 | 1.1 |
| | 242 | 24 | 50 | 13 | 1.1 |
| F | 44 | 12 | 34 | 9 | 1.0 |
| | 92 | 21 | 44 | 16 | 1.0 |
| | 144 | 34 | 53 | 24 | 1.0 |
| | 188 | 49 | 50 | 33 | 0.9 |
| | 252 | 66 | 48 | 48 | 1.1 |
| G | 62 | 72 | 28 | 110 | 0.5 |
| | 104 | 143 | 32 | 185 | 0.7 |
| | 127 | 237 | 32 | 380 | 0.6 |
| | 177 | 359 | 32 | 450 | 0.7 |
| | 223 | 505 | 27 | 630 | 0.8 |

Composition of mixtures.

| Mixture[a] | Coated Aspirin[b] | Cornstarch[c] | Microcrystalline Cellulose[d] | Crospovidone[e] | Modified Starch[f] | Cation-Exchange Resin[g] | Sodium Carboxymethylcellulose[h] |
|---|---|---|---|---|---|---|---|
| A | 0.515 | 0.075 | — | — | — | — | — |
| B | 0.515 | 0.025 | 0.050 | — | — | — | — |
| C | 0.515 | — | — | — | 0.075 | — | — |
| D | 0.515 | — | 0.075 | — | — | — | — |
| E | 0.515 | — | 0.060 | — | — | 0.015 | — |
| F | 0.515 | — | 0.060 | 0.015 | — | — | — |
| G | 0.515 | — | 0.060 | — | — | — | 0.015 |

[a] All mixtures contained 2% (w/w) talc, F.U. grade. [b]Bayer Italy, Milan. [c] F.U. VIII Ed. grade. [d]Elcema G 250, Eigenmann-Veronelli, Milan. [e] Polyplasdone XL, GAF Italy, Milan. [f]STA-RX 1500, Eigenmann Veronelli, Milan. [g]Amberlite IRP 88, C.Erba, Milan. [h]Nymcel ZSB 16, Nyma, Holland.

seems to be the decisive factor. In other cases, the opposite situation is seen. The comparison between C (third compression force level and G (fifth compression force level) mixtures shows that similar $\tau_d$ values correspond to disintegration time values that differ about 50% due to differences in disintegrating force values. The above examples clearly indicate that disintegration time depends on both parameters and only the joint consideration of $F_\infty$ and $\tau_d$ allows an evaluation of the kinetic aspect of the disintegration process. A good correlation was found, on log-log scale, between input and disintegration time (Fig. 3) for all the tablet series examined in Table I.

Other authors (8) have recently examined the effect of recompression (rework) on the swelling force kinetics of tablets made by wet-massing an Avicel® PH 101 matrix containing a fixed percentage of an extra-granular disintegrant (Explotab®, Polyplasdone® XL or Acdisol®).

Although the main aim of the work was to relate disintegrant efficiency to the rework process, the authors could draw interesting conclusion as to the relationship between swelling force development inside tablets and disintegration behaviour. In particular they confirmed that: "The tablet swelling

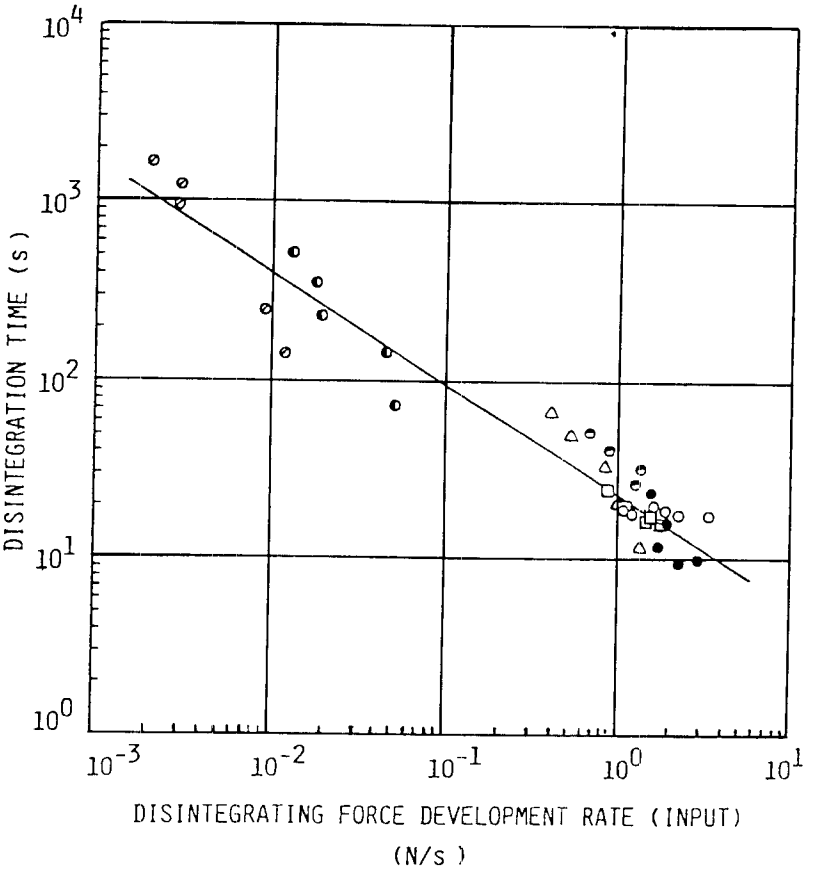


FIGURE 3

Log-log plot of disintegration time versus "input" values. The linear regression equation is log y = -0.6076.log x + 1.3925 (r = 0.968).
Key: (○)A; (□) B; (⊘) C; (◓) D; (●) E; (△) F; (◐) G (6).
(Symbols refer to differing ASA coated tablet formulations examined in Table 1).

(disintegrating) force alone does not control tablet disintegration" and found a correlation, on a log-log scale, between the disintegration time and a composite time function of disintegrating force development. They concluded that

disintegration time is related to the overall kinetics of force development.

All these results confirm the relevance of the kinetics of disintegrating force development to the disintegration process.

## DISINTEGRATION FORCE AND TABLET PROPERTIES

We also investigated the relationships between the force development and various technological parameters and properties such as compression force, porosity and crushing strength (4,6). The maximum force developed in a given formulation generally tends to increase on increasing compression force (4). This observation, formerly made on starch containing formulations (4) (Table 2 ), agreed with the reports of certain authors for whom the starch grain swelling is more effective at reduced porosity values (9) and/or with the observation that in certain formulations the smaller the pore diameter, the greater the capillary pressure developed (10).

On the other hand this phenomenon, observed also in other non starch containing formulations (6) (Table 1), could also be explained by the observation that the swelling or repulsive energy of disintegrators can work best when particles are closer to one another (2).

TABLE 2

Characteristics of ASA Tablets Containing Starch or its Derivatives (4)

| | Force level hN | Hardness N | Porosity % | $y_0$ N | b sec | USP XIX D.T. sec |
|---|---|---|---|---|---|---|
| $ASA_5$ | 56 | 30 | 9.7 | 15.3 | 5"86 | 12" |
| | 159 | 65 | 6.2 | 39 | 30"05 | 18" |
| | 310 | 79 | 6.0 | 46.5 | 53"77 | 32" |
| $ASA_{10}$ | 46 | 12 | 12.7 | 18.3 | 3"08 | 6" |
| | 165 | 65 | 6.9 | 46.2 | 8"51 | 8" |
| | 273 | 72 | 6.4 | 66.6 | 22"33 | 12" |
| $ASA_c$ 3% | 79 | 30 | - | 20.8 | 127" | 112" |
| | 148 | 86 | - | 34.3 | 269" | 210" |
| | 245 | 168 | - | 54.9 | 1049" | 600" |
| $ASA_c$ Elcema | 95 | 26.4 | 10.7 | 64.7 | 14" | 13" |
| | 181 | 45.6 | 8.6 | 71.6 | 21" | 19" |
| | 282 | 53 | 8.0 | 74.5 | 34" | 24" |
| $ASA_c$ Sta-RX | 93 | 22.7 | 13.5 | 15.8 | 13" | 23" |
| | 191 | 54.7 | 10.3 | 14.7 | 31" | 105" |
| | 285 | 66.3 | 9.3 | 14.5 | 70" | 187" |

$y_0$ = maximum disintegrating force
b = time needed for the development of half maximum force
D.T. = disintegration time

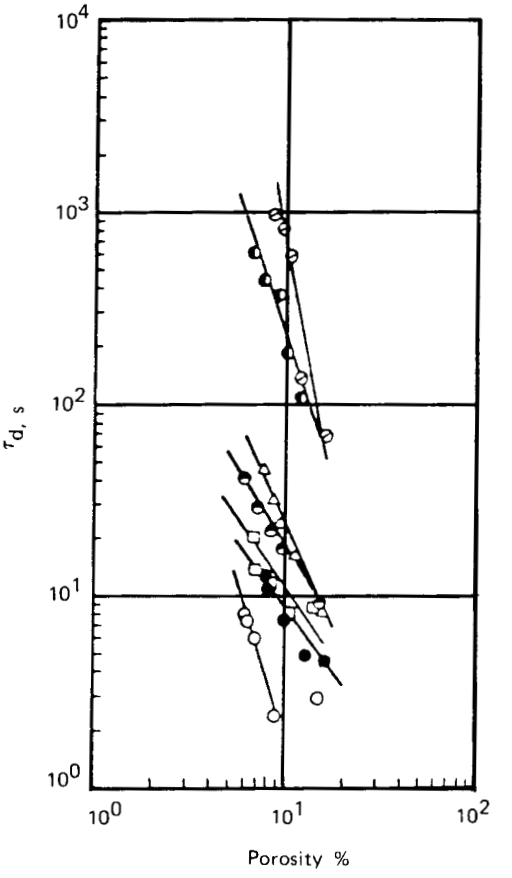


FIGURE 4

Log-log plot of $\tau_d$ values versus porosity. Key (○) A; (□) B; (⊘)C; (◓) D; (●) E; (△) F; (◐) G (6). (See Table 1 for symbols).

The disintegrating force development time (b or $\tau_d$) always increases on increasing compression force (Table 1 and 2) and as porosity decreases (Table 2 and Fig. 4). This is in agreement with the observation that it is related to water penetration (1)

In certain formulations the increase of maximum force developed on increasing compression force may partly compensate the increased value , so that the resultant rate parameter, "input" value (which is the disintegration velocity) is influenced by compression force only to a minor extent.

In fact, the relationships between "input" and compression force depends on the type of formulation (Fig. 5). A complete characterization of the compact can be obtained by plotting crushing strength versus "input" values (Fig. 6), which allows a visual determination of mixtures for which the crushing strength can be increased without significantly reducing the "input" value.

The outcome of all the work done was that the "input" value can be employed as a new parameter for tablet formulation. It is related to disintegration behaviour and it is very sensitive to formulation and tablet structure changes. So, if it is correlated with the crushing strength, it allows an overall evaluation of the formula examined.

As data on disintegrating force became available, we realized that many experimental results concerning the disintegration behaviour of tablets could be fitted very well by the theory of disintegrating force development.

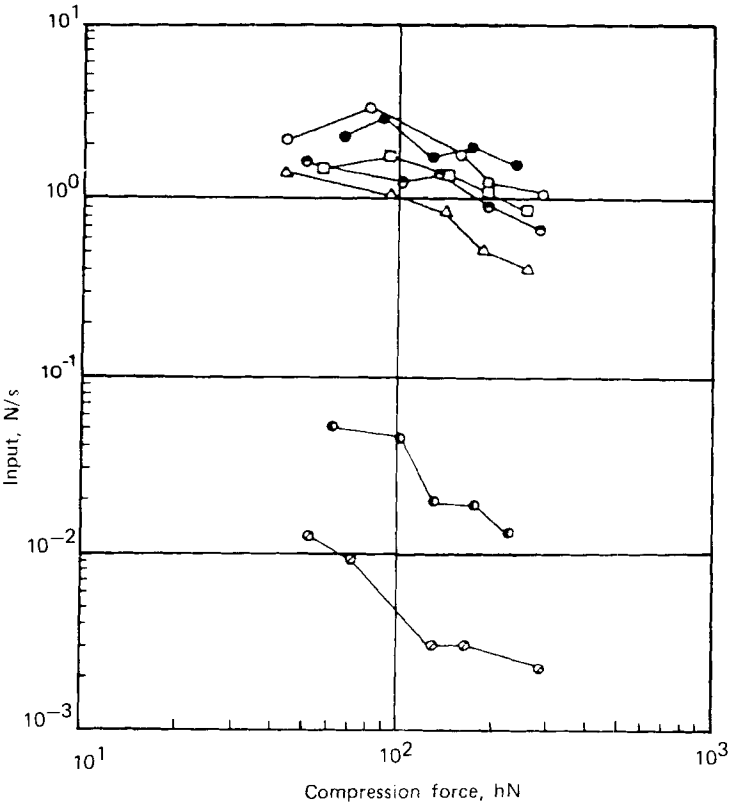


FIGURE 5

Log-log plot of input values versus compression force. Key: (○) A; (□) B; (⊘) C; (◓) D; (●) E; (△) F; (◐) G (6). (See Table 1 for symbols).

## DISINTEGRATION MECHANISMS AND DISINTEGRATING FORCE

When we started investigating disintegrating force development, the mechanisms of disintegrant action had been extensively studied although no conclusive explanation of disintegration process had been advanced.

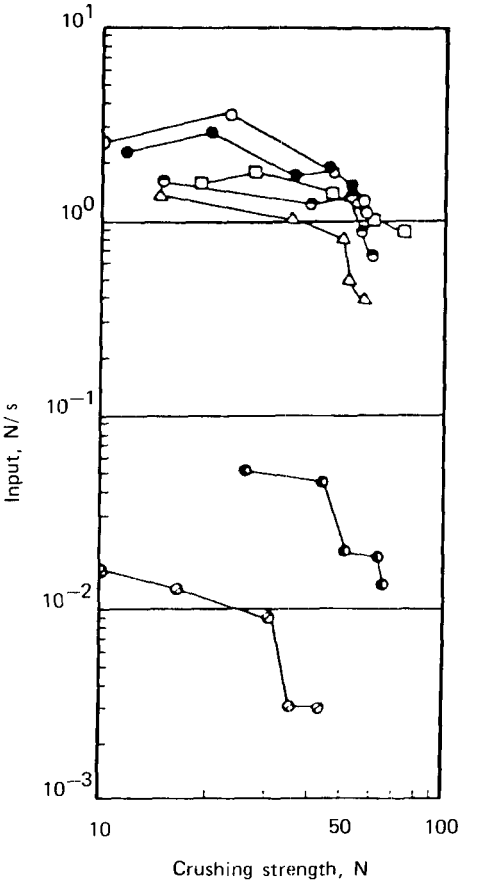


FIGURE 6

Log-log plot of input versus crushing strength. Key: (○) A; (□) B; (⊘) C; (⊖) D; (●) E; (△) F; (◐) G (6).
(See Table 1 for symbols).

At that time many excellent reviews had been published on the mechanisms of disintegrant action (11-13) and many different mechanisms had been proposed, including: swelling (14), deformation (15), capillarity (11), heat of wetting (16),

particle-particle repulsion (17), hydrogen bond annihilation (13) and so on.

Keeping in mind that "a force must develop inside the compact to promote disintegration" (1), we tried to group the various mechanisms on the basis of dynamic considerations, that is on the basis of their capability to promote disintegrating force development. They were grouped in the following manner (1,4):

a) the pressure exerted by the air entrapped in pore structures due to a hydrodynamic process or to the heat of wetting
b) the swelling of the disintegrating agent
c) the repulsion among particles caused by the contact between solid and liquid.

We also stressed the concept that force is not a mechanism by itself but the outcome of a series of events beginning with water penetration and leading to the activation of one of the mechanisms cited. In this perspective, disintegrating force measures might have provided experimental evidence of the existence of certain disintegration mechanisms.

Given these premises and taking advantage of the fact that a relationship had been established in some formulations between

disintegrating force and disintegration time (4,6), we wanted to employ disintegrating force measures to investigate disintegration mechanisms.

We started from swelling and the long lasting discussion dividing the supporters of swelling as an important mechanism of disintegration (2,14), and those who denied its relevance in the disintegration process (13).

Our opinion was that the main argument should not be against swelling itself but against the methods employed for the quantification of the swelling of disintegrant particles.

In fact, of all the tests proposed for the evaluation of swelling properties, only microscopic methods (18,19,20) allowed the direct observation of the increase in disintegrant particle dimensions due to water absorption, whereas all the other methods were based on indirect measurements (hydration capacity, sedimentation volume, expansion of pure disintegrant tablets, water uptake of tablets ....) (21-24). On the other hand, it is wellknown that in most cases (limited swelling materials, particles that tend to deaggregate when submerged in water and so on ..) the increase in particle volume due to swelling can be calculated from the microscopic data with great difficulty.

In order to measure particle volume increase in swelling media we studied the applicability of an instrumental method (Coulter Counter) (25). We validated this method with optical microscopy and concluded that it provided a rapid, accurate and reproducible means for effecting particulate volume measurements both in aqueous and organic media, although with some limitations. It was thought to be especially useful for materials exhibiting a limited swelling, which can be evaluated by microscopic methods with great difficulty.

In fact with this method we were successful in assessing the swelling volume of various disintegrants that had been long discussed from the point of view of their swelling capability (Avicel$^{R}$, native straches, cross-linked polyvinylpyrrolidones..).

Meanwhile (26) we studied the relationship between the swelling properties of various disintegrants and the force development in a tablet formulation based on ASA and containing a fixed percentage of talc (2%) and of each disintegrant (4%).

It was found that the swelling of disintegrant particles play a decisive role in force development: only when a significant swelling of disintegrant particles is present does a measurable force develops inside the tablet (Table 3). Although swelling is needed to produce force, no simple quantitative relationship

could be established between the extent of particle swelling and the amount of force developed.

Subsequently it was put forward that the extent of force developed depends on the type of interaction between material and fluid (type of swelling: molecular, capillar ...) and not on the volume reached by swollen particles (28).

On the other hand disintegration occurred in the formulation examined only when a force was present (Table 3 ). The relationship found, on a log-log scale, between disintegration time and the disintegrating force development rate ("input") for all the ASA tablet series examined (Fig. 7) suggested that swelling, in order to be effective with respect to tablet disintegration, must be capable of promoting the development of a suitable amount of force in a suitable time (26).

These results were subsequently validated also in a formulation based on dicalcium phosphate dihydrate (28).

Almost at the same time, Bolhuis and coworkers (29) were publishing a paper on the action mechanism of modern disintegrants, with particular regard to the influence of lubricants on the disintegration process of a formulation based on dicalcium phosphate dihydrate and containing different

TABLE 3

Relationships Between Particle Swelling of Disintegrants Disintegrating Force and Disintegration Time of ASA tablets. Compression force level 25.5 kN (26, 27).

| Disintegrant (4%) | Immersion fluid | Particle swelling (%) | Disintegrating force (N) | Disintegration time (s) |
|---|---|---|---|---|
| MAIZE STARCH | Isotonic saline | 40 ± 5 | 22.2 ± 3.1 | 26 ± 3 |
| | 0.1 N HCl | 43 ± 5 | 21.8 ± 3.5 | 29 ± 4 |
| | Isopropanol | - | - | - |
| EXPLOTAB® | 0.1 N HCl | 72 ± 17 | 25.3 ± 0.8 | 20 ± 4 |
| | Isopropanol | - | - | - |
| AVICEL® PH 101 | Isotonic saline | 75 ± 14 | 18.6 ± 3.5 | 535 ± 41 |
| | 0.1 N HCl | 69 ± 7 | 16.8 ± 1.3 | 539 ± 35 |
| | Isopropanol | 15 ± 7 | - | - |
| L-HPC® | Isotonic saline | 180 ± 25 | 51.9 ± 1.0 | 18 ± 3 |
| | 0.1 N HCl | 132 ± 11 | 44.1 ± 2.7 | 19 ± 3 |
| | Isopropanol | - | - | - |
| ACDISOL® | 0.1 N HCl | 105 ± 12 | 47.6 ± 3.9 | 9 ± 2 |
| | Isopropanol | - | - | - |
| NYMCEL® ZSB 10 | 0.1 N HCl | 104 ± 12 | 38.5 ± 1.2 | 35 ± 5 |
| | Isopropanol | - | - | - |
| KOLLIDON® CL | Isotonic saline | 195 ± 39 | 18.3 ± 0.9 | 47 ± 6 |
| | 0.1 N HCl | 120 ± 15 | 18.3 ± 2.7 | 45 ± 6 |
| | Isopropanol | 155 ± 27 | 13.7 ± 0.3 | 60 ± 10 |
| POLYPLASDONE® XL | Isotonic saline | 188 ± 23 | 57.1 ± 6.6 | 10 ± 2 |
| | 0.1 N HCl | 109 ± 25 | 55.6 ± 6.8 | 9 ± 2 |
| | Isopropanol | 118 ± 14 | 38.3 ± 0.9 | 43 ± 5 |
| AMBERLITE® IRP 88 | 0.1 N HCl | 57 ± 10 | 70.7 ± 8.0 | 7 ± 2 |
| | Isopropanol | - | - | - |
| EUDISPERT® HV | Isotonic saline | 15 ± 13 | 4.5 ± 2.3 | - |
| | 0.1 N HCl | 21 ± 16 | 9.8 ± 4.1 | - |
| | Isopropanol | - | - | - |

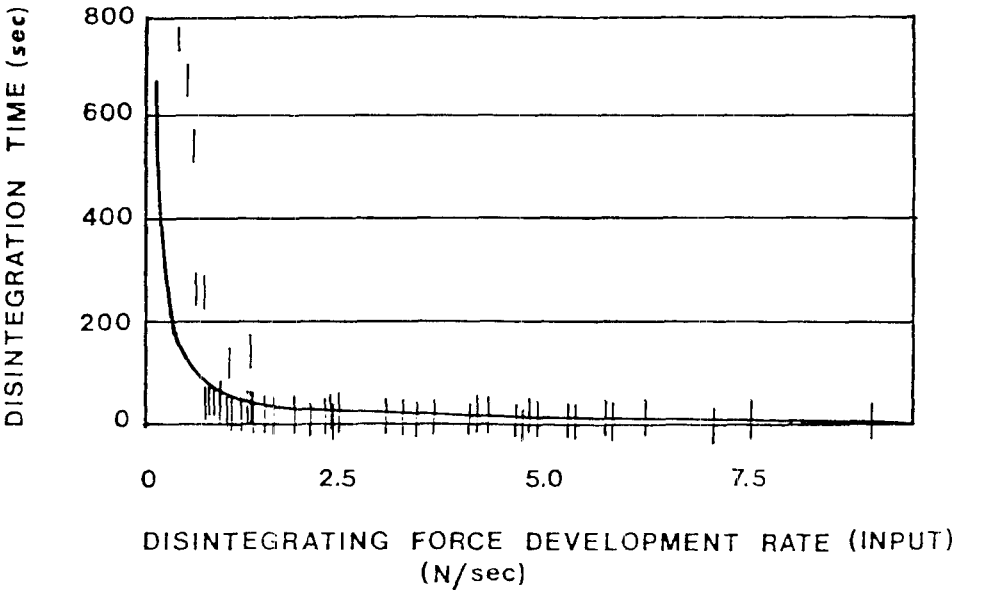


FIGURE 7

Plot of disintegration time versus disintegrating force development rate values for all the ASA tablet series. Brands indicate excperimental points. The equation of the best fitting curve is: $\log y = -1.27 \log x + 1.75$; $r = 0.80$ (26).

disintegrants. They concluded that the swelling capacity of disintegrating agents plays a dominant role in the process of disintegration when an hydrophobic lubricant is incorporated in the tablet, whereas the swelling capacity of the disintegrating agent is of minor importance when no hydrophobic vehicle is present.

They proposed a scheme of disintegrant action for strongly swelling materials suggesting that these disintegrants act not

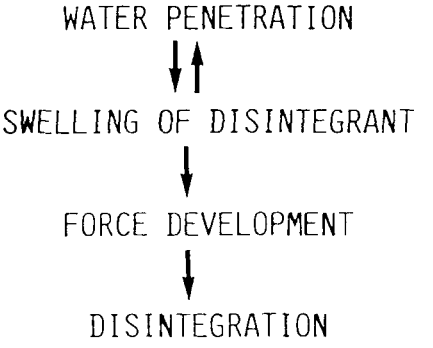


FIGURE 8

Disintegration process scheme (5).

only by promoting water penetration but also by causing a chain reaction of disruption of the tablet.

We enlarged the scheme proposed by Bolhuis and co. by introducing the force development between the various steps (Fig. 8) (5), since, according to our findings, swelling must be capable not only of promoting water penetration (29) but also of producing enough swelling force to cause bond disruption (at least in the formulations examined).

Our conclusion was that "the role of swelling in the disintegration process is to make pore walls hydrophylic so as to provide enough swelling force to produce interparticle bonds disruption. A continuous network formation around the active

principle particles (13) determines efficient disintegration only when it promotes a rapid disintegrating force development" (27).

## MORE ON THE DISINTEGRATION MECHANISM - MOLECULAR SWELLING

While the role of swelling as a dynamic disintegration mechanism (capable of developing a force) had been assessed by means of force measurements (27), experimental evidence supporting or excluding the presence of other dynamic mechanisms (1) was still lacking. In a recent work (28) we tried to quantify by means of force measurements the significance of disintegration mechanisms other than swelling.

In order to do this one tablet formulation, based on dicalcium phosphate dihydrate and containing a fixed percentage of different disintegrants (4%), was checked for both disintegrating force and disintegration time in different environmental conditions, such as are likely to elicit differing disintegration mechanisms.

In particular measures were effected in distilled water at differing temperature and air pressure conditions. Surface tension, density, viscosity, osmotic pressure and water contents of immersion fluid were varied appropriately. The results

obtained indicated that the environmental conditions are likely to influence disintegrating force development only when they are capable of influencing the swelling properties of disintegrants. In particular in all the situations in which water was available in lesser quantity (for example in water-ethanol mixtures (Fig. 9)) or at a slower rate (for example, on increasing immersion fluid viscosity (Fig. 10)) to the disintegrant particles, force development decreased and disintegration time increased. These effects were more marked for those disintegrants that require much water in order to swell, owing to their high swelling volume (e.g. Primojel® and Acdisol® ). By contrast, the efficiency of disintegrants like Polyplasdone® XL and Amberlite® IRP 88 was less influenced by the reduced water availability owing to the fact that they develop a high swelling force despite a low swelling volume. These findings are also going to be validated in other tablet formulations based on different materials.

The results so far obtained, besides supporting the hypothesis of particle swelling mechanism in the disintegration process (at least in the formulation examined), also suggested further investigation of swelling at a molecular level.

In order to do this a molecular model should be developed attempting to relate the chemico-physical properties of swelling

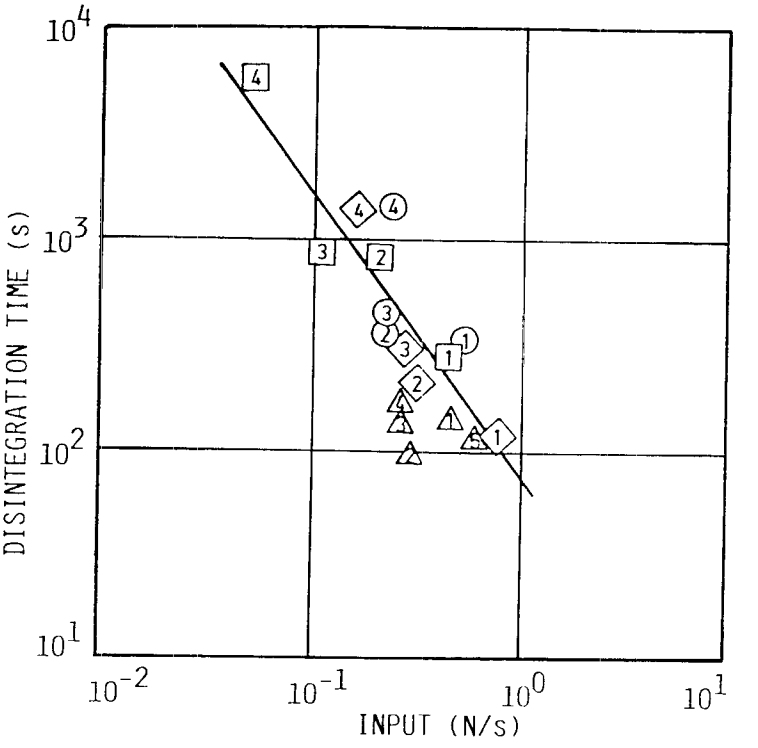


FIGURE 9

Relationship between disintegration time and "input" of dibasic calcium phosphate tablets.
Figures within the symbols indicate the decreasing order of water contents of immersion fluid (water-ethanol mixture) (Primojel$^R$ □ ; Ac-Di-Sol$^R$ ◇; Polyplasdone$^R$ XL △ ; Amberlite$^R$ IRP 88 ○) (28).
Note that in Polyplasdone$^R$ XL containing tablets force development is scarsely influenced by water contents, since Polyplasdone$^R$ XL swelling is also activated in alcohols.

materials to the amount of water penetrated and the amount of force developed.

A better understanding of swelling at a molecular level should also prove useful for the comprehension of other

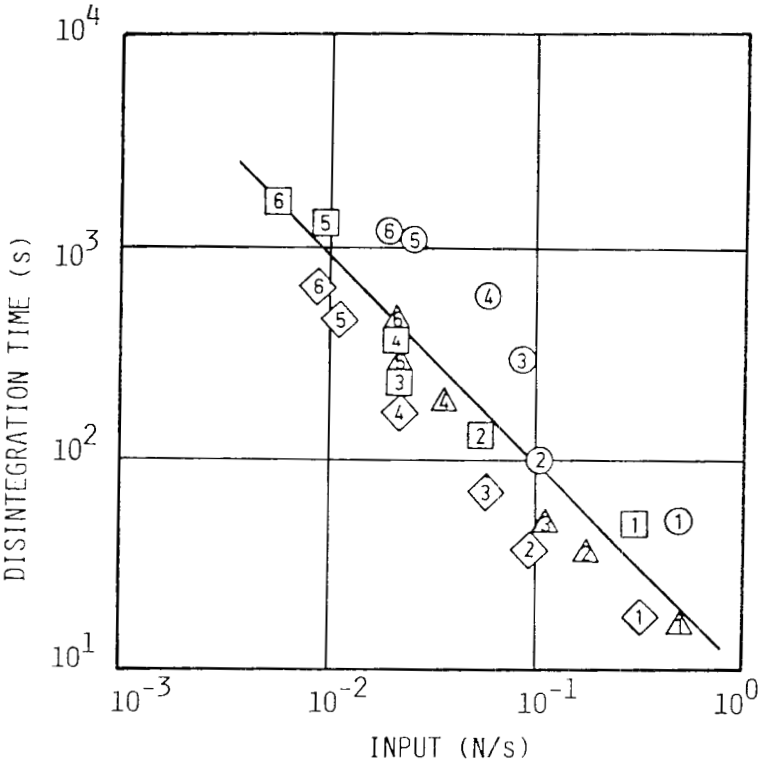


FIGURE 10

Relationship between disintegration time and "input" of dibasic calcium phosphate tablets.
Figures within the symbols indicate the increasing order of immersion fluid viscosity.
(Primojel® □ ; Ac-Di-Sol® ◇ ; Polyplasdone® XL △; Amberlite® IRP 88 ○) (28).

swelling-controlled phenomena such as the controlled release of active principles (30).

## WATER PENETRATION AND DISINTEGRATING FORCE

The two schemes proposed for the disintegration process, one based on water penetration (29) and the other on force

development (5,28), seemed to provide the same kind of information at least in the case of insoluble formulations (31). However it was felt that they should not necessarily apply to other kinds of tablet formulations, in particular to soluble ones. In fact, preliminary studies had indicated that, in tablet formulations where the base material is soluble in the immersion fluid, such as, for example, glucose in water or ASA in alcohols, disintegrating force development was hindered (5) (Fig. 11). Moreover, the very interesting papers, published by Lerk and co. on the disintegration and dissolution pattern of different kinds of lactose (32) had proved that, besides active mechanisms (that is those capable of developing a disintegrating force), also passive mechanisms, (that is those capable of weakening interparticle bonds without developing repulsion between particles), may be responsible for disintegration process.

It was believed that, when passive mechanisms (such as hydrogen bond annihilation) are also present, a poor correlation between disintegrating force parameters and disintegration time was to be expected and that water penetration measurements should be better related to disintegration behaviour.

Consequently we combined water penetration and disintegrating force measurements in differing tablet base materials

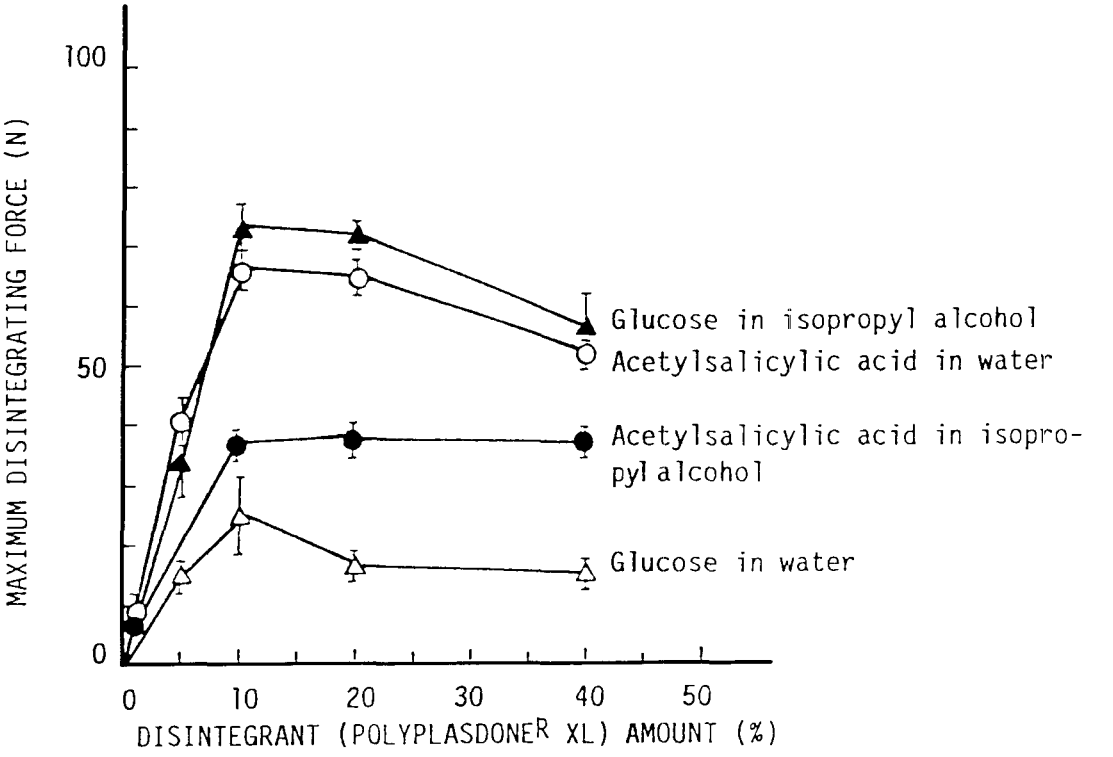


FIGURE 11

Effect of tablet base material solubility on disintegrating force development (5).
Polyplasdone® XL was chosen as a disintegrant since its swelling is also activated in alcohol.

(water-soluble, hydrophilic and hydrophobic) such as were likely to elicit different disintegration mechanisms.

Such a study allowed us to assess the role played by active and passive mechanisms in the disintegration process (33).

Subsequently (34), to provide a general model describing the relationships between water uptake, force development and

disintegration time depending on the base material employed, we set up a "designed" experiment. Different tablet series were chosen made from either dicalcium phosphate dihydrate or acetylsalicylic acid or $\alpha$-lactose monohydrate or $\beta$-lactose. Three disintegrants with differing swelling properties and employed in varying percentages, so as to modify formula hydrophylicity opportunely, were chosen.

Data relative to these tablet series, that is disintegration time, disintegrating force development rate and water penetration rate (expressed, in analogy with force measures, by an instantaneous value of water penetration rate (32)), were treated by multiple regression analysis effected on the log transform of both dependent variable (disintegration time) and independent variables (disintegrating force development rate and water penetration rate). Additional "dummy" and interaction variables were added to the model to take into account the type of base material employed and the possible interactions between the material employed and the measure effected.

Multiple regression calculations were effected using the "new regression" procedure of the SSPS program. Independent variables were entered into the regression equation in the following order:

water penetration rate, disintegrating force development rate, "dummy" variables and interaction variables. As each new variable was considered its inclusion in the final regression equation was decided on the basis of a statistical test, depending on whether it contributed significantly to the regression relationship or not.

It was found that the relationship between disintegration time, disintegrating force development rate and water penetration rate depended on the type of base material employed and in particular on its solubility characteristics. In any case, entering disintegrating force measures besides water penetration measurements significantly improved the regression relationship, even in the case of soluble materials, thus allowing us to differentiate among different materials.

The predictive power of the regression model obtained shall be validated on other tablet formulations.

## CONCLUSIVE REMARKS

So far, we got to certain conclusions concerning the relationships between water penetration, force development and disintegration. Although the results are reasonably applicable to

different kinds of formulations, they provide only a phenomenological description of the disintegration process.

The future development of this research should be aimed at two main goals: a theoretical goal, that is to provide a more physical explanation (30) of the disintegration process; a practical goal, that is to assist tablet formulatoirs in the choice of an individualized disintegrant for every tablet base material.

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